
FILE 'ADISCTI, BIOSIS, BIOTECHNO, CAPLUS, DRUGU, EMBASE, FEDRIP, IFIPAT, JICST-EPLUS, LIFESCI, MEDLINE, PASCAL, SCISEARCH, TOXCENTER, WPIDS'
ENTERED AT 21:13:58 ON 01 APR 2004

```
L2         61582 S L1
L3           484 S L2 AND INSULIN(P)(RESIST? OR SENSITIV?)
L4           315 S L3 AND (OBES? OR HYPERTENS? OR HIGH(2A)BLOOD(2A)PRESSUR? OR
L5           143 DUP REM L4 (172 DUPLICATES REMOVED)
L6            26 S L5 AND PY<=1998
L7          8005 S L2 AND (OBES? OR HYPERTENS? OR HIGH(2A)BLOOD(2A)PRESSUR? OR
L8          5836 S L2 AND (OBES? OR HYPERTENS? OR HIGH(2A)BLOOD(2A)PRESSUR? OR
L9           712 S L8 AND INSULIN?
L10          330 DUP REM L9 (382 DUPLICATES REMOVED)
L11           98 S L10 AND PY<=1998
L12          686 S L9 NOT L6
L13           73 S L11 NOT L6

=> s l2 (p) (obes? or hypertens? or high(2a)blood(2a)pressur? or liver? or hepatic?
or diabet?)
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L4  (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L8  (P) '
   9 FILES SEARCHED...
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L13 (P) '
L14        5974 L2 (P) (OBES? OR HYPERTENS? OR HIGH(2A) BLOOD(2A) PRESSUR? OR
                LIVER? OR HEPATIC? OR DIABET?)
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FILE 'WPINDEX' ACCESS NOT AUTHORIZED

=>
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=> s l1
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH

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FIELD CODE - 'AND' OPERATOR ASSUMED 'OXID?(P)(DONOR?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'OXID?(P)(DONOR?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'OXID?(P)(DONOR?'
  12 FILES SEARCHED...
L2        61582 L1
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nitric (3a) oxide (p) (donor? or agonist?)

```
=> s l2 and insulin(p)(resist? or sensitiv?)
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FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)(RESIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)(RESIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'INSULIN(P)(RESIST?'
  12 FILES SEARCHED...
L3          484 L2 AND INSULIN(P)(RESIST? OR SENSITIV?)

=> s l3 and (obes? or hypertens? or high(2a)blood(2a)pressur? or liver? or hepatic?
or diabet?)
   9 FILES SEARCHED...
L4          315 L3 AND (OBES? OR HYPERTENS? OR HIGH(2A) BLOOD(2A) PRESSUR? OR
              LIVER? OR HEPATIC? OR DIABET?)

=> dup rem l4
DUPLICATE IS NOT AVAILABLE IN 'FEDRIP'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L4
L5           143 DUP REM L4 (172 DUPLICATES REMOVED)

=> s l5 and py<=1998
   3 FILES SEARCHED...
   6 FILES SEARCHED...
'1998' NOT A VALID FIELD CODE
  11 FILES SEARCHED...
  12 FILES SEARCHED...
  14 FILES SEARCHED...
L6          26 L5 AND PY<=1998

=> d l6 abs ibib kwic 1-26

L6   ANSWER 1 OF 26  ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN
ACCESSION NUMBER:    1996:6231  ADISCTI
DOCUMENT NUMBER:     800447403
TITLE:               Metabolic effects of intravenous L-arginine in patients
                     with non insulin- dependent diabetes mellitus.
AUTHOR:              Wascher T C; Graier W F; Bahadori B; Diabetic Angiopathy
                     Research Group; et  al.
SOURCE:              European Journal of Clinical Investigation (Jan 1, 1996),
                     Vol. 26 (Suppl. 1), pp. 40
DOCUMENT TYPE:       Citation
REFERENCE:           Diabetes
FILE SEGMENT:        Citation
LANGUAGE:            English
PY   1996
TI   Metabolic effects of intravenous L-arginine in patients with non insulin-
     dependent diabetes mellitus.
CT   Drug Descriptors: Arginine, pharmacodynamics; Amino acids,
     pharmacodynamics; Neurotransmitter agonists, pharmacodynamics;
```

Nitric oxide agonists, pharmacodynamics;
Nitric oxide donors, pharmacodynamics
CT Disease Descriptors: **Diabetic** angiopathies; Cardiovascular disorders; **Diabetic** complications; Endocrine disorders; Vascular disorders; **Insulin resistance**; Metabolic disorders; Metabolic syndrome; Type 2 **diabetes** mellitus; **Diabetes** mellitus

L6 ANSWER 2 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AB Several **hypertensive** states are associated with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiological importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, we sought to determine how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist**-stimulated intracellular Ca2+ (Cai2+) transient in VSM cells. In this study, our goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Cai2+ and, if so, to determine whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP.
Primary cultured VSM cells from canine femoral artery were bathed in a physiological concentration of extracellular Ca2+ and permeabilized to Ca2+ with a Ca2+ ionophore, either ionomycin or A-23187. The resultant increase in Cai2+ contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Cai2+ or the ionomycin-induced increase in Ci2+, as determined by fura 2 fluorescence measurements, but it did inhibit ionomycin- and A-23187-induced contractions by 47 and 51%, respectively (both $P < 0.05$). In the presence of 1.0 muM ionized Ca2+, ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP production by 43% ($P < 0.05$). 1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one (10 muM), a selective inhibitor of guanylate cyclase that blocked cGMP production in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. It was found that the cells expressed the inducible isoform of NOS. NG-monomethyl-Larginine or NG-nitro-L-arginine methyl ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. We conclude that **insulin** stimulates cGMP production and inhibits VSM contraction in the presence of elevated Cai2+. This inhibition by **insulin** of VSM contraction at sites where Cai2+ could not be rate limiting is dependent on NOS and cGMP.
ACCESSION NUMBER: 1998:298726 BIOSIS
DOCUMENT NUMBER: PREV199800298726
TITLE: Insulin inhibits vascular smooth muscle contraction at a site distal to intracellular Ca2+ concentration.
AUTHOR(S): Kahn, Andrew M. [Reprint author]; Husid, Annat; Odebunmi, Timothy; Allen, Julius C.; Seidel, Charles L.; Song, Tom
CORPORATE SOURCE: 4.138 MSB, Univ. Texas Health Sci. Cent., P.O. Box 20708, Houston, TX 77225, USA
SOURCE: American Journal of Physiology, (May, 1998) Vol. 274, No. 5 PART 1, pp. E885-E892. print.
CODEN: AJPHAP. ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English

ENTRY DATE: Entered STN: 15 Jul 1998
Last Updated on STN: 15 Jul 1998
SO American Journal of Physiology, (May, 1998) Vol. 274, No. 5 PART 1, pp. E885-E892. print.
CODEN: AJPHAP. ISSN: 0002-9513.

AB Several **hypertensive** states are associated with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiological importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, we sought to determine how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist**-stimulated intracellular Ca2+ (Cai2+) transient in VSM cells. In this study, our goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Cai2+ and, if so, to determine whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP. Primary cultured VSM cells from canine femoral artery were bathed in a physiological concentration of extracellular. . . ionomycin or A-23187. The resultant increase in Cai2+ contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Cai2+ or the ionomycin-induced increase in Ci2+, as determined by fura 2 fluorescence. . . and 51%, respectively (both $P < 0.05$). In the presence of 1.0 muM ionized Ca2+, ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP production by 43% ($P < 0.05$). 1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one (10 muM), a selective inhibitor of guanylate cyclase that blocked cGMP production in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. It was found that the cells expressed the inducible isoform of NOS. NG-monomethyl-Larginine or NG-nitro-L-arginine methyl ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. We conclude that **insulin** stimulates cGMP production and inhibits VSM contraction in the presence of elevated Cai2+. This inhibition by **insulin** of VSM contraction at sites where Cai2+ could not be rate limiting is dependent on NOS and cGMP.

L6 ANSWER 3 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB 1. The effects of **nitric oxide** (NO) on vascular reactivity and platelet function in the **obese** (cp/cp) and lean (+/?) JCR:LA-cp rats were investigated. 2. Phenylephrine (PE; 0.1 nM-10 muM) induced contraction of isolated aortic rings in both genotypes (cp/cp and +/?) of JCR:LA-cp rats. The **sensitivity** to contraction with PE was enhanced in cp/cp compared with +/? rings. Rings from both genotypes showed an increased contraction upon removal of the endothelium. 3. Acetylcholine (ACh; 0.1 nM-10 muM)-induced endothelium-dependent relaxation of rings was not significantly different in the two genotypes. Both were inhibited to a similar extent by NG-nitro-L-arginine methyl ester (L-NAME; 0.01-1 mM) when administered in vitro. 4. The **nitric oxide** synthase (NOS) inhibitor (L-NAME; 0.3, 1 or 3 mg ml-1, p.o.) when administered in vivo increased blood pressure in cp/cp rats but not in +/? rats. 5. L-NAME resulted in greater inhibition of ACh-induced relaxation in cp/cp rings compared with +/? rings. 6. L-NAME treatment in vivo caused a decrease in cyclic GMP and NOS activity in rings from cp/cp but not + /? rats. 7. The NO **donor**,

S-nitroso-N-acetyl-DL-penicillamine (SNAP; 0.1 nM-10 muM)-induced relaxation of rings from +/? rats, an effect enhanced by the treatment with L-NAME in vivo. 8. Oral administration of L-NAME did not enhance the vasorelaxant effect of SNAP on rings of aorta from cp/cp animals. 9. Platelet aggregation and NOS activity were similar in both genotypes and were not modified by oral administration of L-NAME. 10. These results show that unimpaired generation of NO is crucial for maintenance of vascular tone particularly under conditions of vascular insult exemplified by **insulin resistance**, **obesity** and dyslipidemia detected in cp/cp rats.

ACCESSION NUMBER: 1998:298051 BIOSIS
DOCUMENT NUMBER: PREV199800298051
TITLE: Inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, **obese** JCR:LA-cp rats.
AUTHOR(S): McKendrick, Joyce D.; Salas, Eduardo; Dude, Gregory P.; Murat, Jesus; Russell, James C.; Radomski, Marek W. [Reprint author]
CORPORATE SOURCE: Dep. Pharmacol., Univ. Alberta, Emdonton, AB T6G 2H7, Canada
SOURCE: British Journal of Pharmacology, (May, 1998) Vol. 124, No. 2, pp. 361-369. print.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jul 1998
Last Updated on STN: 15 Jul 1998

TI Inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, **obese** JCR:LA-cp rats.

SO British Journal of Pharmacology, (May, 1998) Vol. 124, No. 2, pp. 361-369. print.
CODEN: BJPCBM. ISSN: 0007-1188.

AB 1. The effects of **nitric oxide** (NO) on vascular reactivity and platelet function in the **obese** (cp/cp) and lean (+/?) JCR:LA-cp rats were investigated. 2. Phenylephrine (PE; 0.1 nM-10 muM) induced contraction of isolated aortic rings in both genotypes (cp/cp and +/?) of JCR:LA-cp rats. The **sensitivity** to contraction with PE was enhanced in cp/cp compared with +/? rings. Rings from both genotypes showed an increased contraction. . . Both were inhibited to a similar extent by NG-nitro-L-arginine methyl ester (L-NAME; 0.01-1 mM) when administered in vitro. 4. The **nitric oxide** synthase (NOS) inhibitor (L-NAME; 0.3, 1 or 3 mg ml-1, p.o.) when administered in vivo increased blood pressure in cp/cp. . . a decrease in cyclic GMP and NOS activity in rings from cp/cp but not + /? rats. 7. The NO **donor**, S-nitroso-N-acetyl-DL-penicillamine (SNAP; 0.1 nM-10 muM)-induced relaxation of rings from +/? rats, an effect enhanced by the treatment with L-NAME in. . . that unimpaired generation of NO is crucial for maintenance of vascular tone particularly under conditions of vascular insult exemplified by **insulin resistance**, **obesity** and dyslipidemia detected in cp/cp rats.

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
JCR:LA-cp rat: **insulin-resistant**, **obese**
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L6 ANSWER 4 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB We investigated whether endothelial function may be impaired in the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, a model of spontaneous NIDDM. The effect of exercise training and food restriction on endothelial function was also studied. OLETF rats were divided into three groups at age 16 weeks: sedentary, exercise trained, and food restricted (70% of the food intake of sedentary rats). Otsuka Long-Evans Tokushima rats were used as the age-matched nondiabetic controls. Endothelium-dependent relaxation of the thoracic aorta induced by histamine was significantly attenuated in the sedentary or food-restricted rats, and exercise training improved endothelial function. Relaxation induced by sodium nitroprusside, a **donor** of **nitric oxide**, did not differ significantly among groups. Both exercise training and food restriction significantly suppressed plasma levels of glucose and **insulin** and serum levels of triacylglycerol and cholesterol and reduced the accumulation of abdominal fat. **Insulin sensitivity**, as measured by the hyperinsulinemic-euglycemic clamp technique, was significantly decreased in sedentary rats but was enhanced in exercise-trained and food-restricted rats. The urinary excretion of nitrite was significantly decreased in sedentary and food-restricted rats compared with nondiabetic rats and was significantly increased in exercise-trained rats. These results indicate that exercise training, but not food restriction, prevents endothelial dysfunction in NIDDM rats, presumably due to the exercise-induced increase in the production of **nitric oxide**.

ACCESSION NUMBER: 1998:91693 BIOSIS
DOCUMENT NUMBER: PREV199800091693
TITLE: Effect of exercise training and food restriction on endothelium-dependent relaxation in the Otsuka Long-Evans Tokushima Fatty rat, a model of spontaneous NIDDM.
AUTHOR(S): Sakamoto, Sadaichi; Minami, Kazushi; Niwa, Yasuharu; Ohnaka, Masaharu; Nakaya, Yutaka [Reprint author]; Mizuno, Akira; Kuwajima, Masamichi; Shima, Kenji
CORPORATE SOURCE: Dep. Nutrition, Sch. Med., Univ. Tokushima, 3-18-15 Kuramoto-cho, Tokushima City 770, Japan
SOURCE: Diabetes, (Jan., 1998) Vol. 47, No. 1, pp. 82-86. print. CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Feb 1998
Last Updated on STN: 25 Feb 1998
SO Diabetes, (Jan., 1998) Vol. 47, No. 1, pp. 82-86. print.
CODEN: DIAEAZ. ISSN: 0012-1797.

AB. . . significantly attenuated in the sedentary or food-restricted rats, and exercise training improved endothelial function. Relaxation induced by sodium nitroprusside, a **donor** of **nitric oxide**, did not differ significantly among groups. Both exercise training and food restriction significantly suppressed plasma levels of glucose and **insulin** and serum levels of triacylglycerol and cholesterol and reduced the accumulation of abdominal fat. **Insulin sensitivity**, as measured by the hyperinsulinemic-euglycemic clamp technique, was significantly decreased in sedentary rats but was enhanced in exercise-trained and food-restricted. . . but not food restriction, prevents endothelial dysfunction in NIDDM rats, presumably due to the exercise-induced increase in the production of **nitric oxide**.

IT . . .
Cardiovascular System (Transport and Circulation); Endocrine System

(Chemical Coordination and Homeostasis); Nutrition
IT Diseases
atherosclerosis: vascular disease
Arteriosclerosis (MeSH)
IT Diseases
diabetes mellitus: endocrine disease/pancreas, metabolic disease
Diabetes Mellitus (MeSH)
IT Diseases
non-insulin-dependent **diabetes** mellitus: endocrine disease/pancreas, metabolic disease, spontaneous
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)
IT Chemicals & Biochemicals
cholesterol; glucose; insulin; nitric oxide; nitrite: urinary excretion; triacylglycerol

L6 ANSWER 5 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AB **Nitric oxide** activates guanylate cyclase to form cGMP, composing a signalling system that is believed to be a distinct mechanism for increasing glucose transport and metabolism in skeletal muscle. The effects of a selective cGMP phosphodiesterase inhibitor, zaprinast, on basal glucose utilization was investigated in incubated rat soleus muscle preparations isolated from both **insulin-sensitive** (lean Zucker; Fa/?) and **insulin-resistant** (**obese** Zucker; fa/fa) rats. Zaprinast at 27 muM significantly increased cGMP levels in incubated soleus muscle isolated from lean, but not **obese**, Zucker rats. Muscles were incubated with 14C-labelled glucose and various concentrations of zaprinast (3, 27 and 243 muM). Zaprinast (at 27 and 243 muM) significantly increased rates of net and 14C-labelled lactate release and of glycogen synthesis in lean Zucker rat soleus muscle; glucose oxidation was also increased by 27 muM zaprinast. In addition, regardless of concentration, the phosphodiesterase inhibitor failed to increase any aspect of 14C-labelled glucose utilization in soleus muscles isolated from **obese** Zucker rats, The maximal activity of **nitric oxide** synthase (NOS) was significantly decreased in **insulin-resistant** **obese** Zucker muscles. Thus the lack of effect of zaprinast in **insulin-resistant** skeletal muscle is consistent with decreased NOS activity. To test whether there is a defect in **insulin-resistant** skeletal muscle for endogenous activation of guanylate cyclase, soleus muscles were isolated from both **insulin-sensitive** and **insulin-resistant** Zucker rats and incubated with various concentrations of the NO **donor** sodium nitroprusside (SNP; 0.1, 1, 5 and 15 mM). SNP significantly increased rates of net and 14C-labelled lactate release, as well as glucose oxidation in muscles isolated from both **insulin-sensitive** and **insulin-resistant** rats. A decreased response to SNP was observed in the dose-dependent generation of cGMP within isolated soleus muscles from **insulin-resistant** rats. A possible link between impaired NO/cGMP signalling and abnormal glucose utilization by skeletal muscle is discussed.
ACCESSION NUMBER: 1998:88113 BIOSIS
DOCUMENT NUMBER: PREV199800088113
TITLE: Evidence for altered **sensitivity** of the nitric oxide/cGMP signalling cascade in **insulin-resistant** skeletal muscle.
AUTHOR(S): Young, Martin E.; Leighton, Brendan [Reprint author]
CORPORATE SOURCE: Dep. Biochem., Univ. Oxford, South Parks Rd., Oxford OX1

3QU, UK
SOURCE: Biochemical Journal, (Jan. 1, 1998) Vol. 329, No. 1, pp. 73-79. print.
ISSN: 0264-6021.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Feb 1998
Last Updated on STN: 25 Feb 1998

TI Evidence for altered **sensitivity** of the nitric oxide/cGMP signalling cascade in **insulin-resistant** skeletal muscle.

SO Biochemical Journal, (Jan. 1, 1998) Vol. 329, No. 1, pp. 73-79. print.
ISSN: 0264-6021.

AB **Nitric oxide** activates guanylate cyclase to form cGMP, composing a signalling system that is believed to be a distinct mechanism for increasing. . . selective cGMP phosphodiesterase inhibitor, zaprinast, on basal glucose utilization was investigated in incubated rat soleus muscle preparations isolated from both **insulin-sensitive** (lean Zucker; Fa/?) and **insulin-resistant** (**obese** Zucker; fa/fa) rats. Zaprinast at 27 muM significantly increased cGMP levels in incubated soleus muscle isolated from lean, but not **obese**, Zucker rats. Muscles were incubated with 14C-labelled glucose and various concentrations of zaprinast (3, 27 and 243 muM). Zaprinast (atomic . . regardless of concentration, the phosphodiesterase inhibitor failed to increase any aspect of 14C-labelled glucose utilization in soleus muscles isolated from **obese** Zucker rats, The maximal activity of **nitric oxide** synthase (NOS) was significantly decreased in **insulin-resistant obese** Zucker muscles. Thus the lack of effect of zaprinast in **insulin-resistant** skeletal muscle is consistent with decreased NOS activity. To test whether there is a defect in **insulin-resistant** skeletal muscle for endogenous activation of guanylate cyclase, soleus muscles were isolated from both **insulin-sensitive** and **insulin-resistant** Zucker rats and incubated with various concentrations of the NO **donor** sodium nitroprusside (SNP; 0.1, 1, 5 and 15 mM). SNP significantly increased rates of net and 14C-labelled lactate release, as well as glucose oxidation in muscles isolated from both **insulin-sensitive** and **insulin-resistant** rats. A decreased response to SNP was observed in the dose-dependent generation of cGMP within isolated soleus muscles from **insulin-resistant** rats. A possible link between impaired NO/cGMP signalling and abnormal glucose utilization by skeletal muscle is discussed.

IT Major Concepts
Biochemistry and Molecular Biophysics

IT Parts, Structures, & Systems of Organisms
skeletal muscle, **insulin-resistant**

IT Chemicals & Biochemicals
cGMP [cyclic GMP]; guanylate cyclase; nitric oxide; nitric oxide synthase

L6 ANSWER 6 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB To investigate whether **insulin** effect on endothelium is related to a specific signal transduction pathway or reflects a more generalized action of the hormone, we studied in aortic rings of Wistar-Kyoto (WKY) rats the effects of the hormone on endothelium-dependent relaxations generated by acetylcholine, adenosine diphosphate, the selective alpha2-adrenergic **agonist** UK 14,304, and the calcium ionophore

ionomycin. The responses were evaluated both in control conditions and after 30 minutes of exposure to three different levels of **insulin** (30, 100, and 500 muU/mL). **Insulin** failed to modify the phenylephrine aortic contractions and the relaxations induced by acetylcholine, adenosine diphosphate, and ionomycin. In contrast, both 100 and 500 muU/mL **insulin** were able to potentiate the UK 14,304-induced vasorelaxation (+96+-19% and + 91 +- 12%, respectively). Pertussis toxin, which causes alpha2-adrenergic receptor Gi uncoupling, reduced the alpha2-adrenergic vasorelaxation and prevented the **insulin** potentiation of the response to UK 14,304. Furthermore, in primary cultured aortic endothelial cells from WKY, we evaluated the conversion of (3H)arginine to (3H)citrulline in response to acetylcholine, ionomycin, and UK 14,304, both in control conditions and during **insulin** exposure. Again, **insulin** did not affect basal citrulline production or the increase induced by acetylcholine and ionomycin, whereas it potentiated the response to UK 14,304. Finally, in aortic rings of spontaneously **hypertensive** rats, **insulin** treatment (100 and 500 muU/mL) was unable to enhance the alpha2-adrenergic vasodilator response; in vascular endothelial cells from spontaneously **hypertensive** rats, **insulin** did not potentiate the increase in citrulline production evoked by UK 14,304. In conclusion, **insulin** selectively enhances alpha2-adrenergic endothelial vasorelaxation through a pertussis toxin-**sensitive** mechanism, by potentiating endothelial **nitric oxide** production. This vasorelaxant mechanism is altered in spontaneously **hypertensive** rats.

ACCESSION NUMBER: 1998:4119 BIOSIS
DOCUMENT NUMBER: PREV199800004119
TITLE: Insulin enhances endothelial alpha2-adrenergic vasorelaxation by a pertussis toxin mechanism.
AUTHOR(S): Lembo, Giuseppe; Iaccarino, Guido; Vecchione, Carmine; Barbato, Emanuele; Morisco, Carmine; Monti, Francesco; Parrella, Lucia; Trimarco, Bruno [Reprint author]
CORPORATE SOURCE: Dep. Internal Med., "Federico II" Univ., Via Pansini 5, 80131 Naples, Italy
SOURCE: Hypertension (Dallas), (Nov., 1997) Vol. 30, No. 5, pp. 1128-1134. print.
CODEN: HPRTDN. ISSN: 0194-911X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Dec 1997
Last Updated on STN: 23 Dec 1997
SO Hypertension (Dallas), (Nov., 1997) Vol. 30, No. 5, pp. 1128-1134. print.
CODEN: HPRTDN. ISSN: 0194-911X.
AB To investigate whether **insulin** effect on endothelium is related to a specific signal transduction pathway or reflects a more generalized action of the hormone,. . . of Wistar-Kyoto (WKY) rats the effects of the hormone on endothelium-dependent relaxations generated by acetylcholine, adenosine diphosphate, the selective alpha2-adrenergic **agonist** UK 14,304, and the calcium ionophore ionomycin. The responses were evaluated both in control conditions and after 30 minutes of exposure to three different levels of **insulin** (30, 100, and 500 muU/mL). **Insulin** failed to modify the phenylephrine aortic contractions and the relaxations induced by acetylcholine, adenosine diphosphate, and ionomycin. In contrast, both 100 and 500 muU/mL **insulin** were able to potentiate the UK 14,304-induced vasorelaxation (+96+-19% and + 91 +- 12%, respectively). Pertussis toxin, which causes alpha2-adrenergic receptor Gi uncoupling, reduced the alpha2-adrenergic vasorelaxation and prevented the **insulin**

potentiation of the response to UK 14,304. Furthermore, in primary cultured aortic endothelial cells from WKY, we evaluated the conversion of (3H)arginine to (3H)citrulline in response to acetylcholine, ionomycin, and UK 14,304, both in control conditions and during **insulin** exposure. Again, **insulin** did not affect basal citrulline production or the increase induced by acetylcholine and ionomycin, whereas it potentiated the response to UK 14,304. Finally, in aortic rings of spontaneously **hypertensive** rats, **insulin** treatment (100 and 500 muU/mL) was unable to enhance the alpha2-adrenergic vasodilator response; in vascular endothelial cells from spontaneously **hypertensive** rats, **insulin** did not potentiate the increase in citrulline production evoked by UK 14,304. In conclusion, **insulin** selectively enhances alpha2-adrenergic endothelial vasorelaxation through a pertussis toxin-**sensitive** mechanism, by potentiating endothelial **nitric oxide** production. This vasorelaxant mechanism is altered in spontaneously **hypertensive** rats.

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
spontaneously **hypertensive** rat: male
Wistar-Kyoto rat: male
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L6 ANSWER 7 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB Cardiac allograft vasculopathy (CAV) remains a troublesome long-term complication of heart transplantation. it is manifested by a unique and unusually accelerated form of coronary disease affecting both intramural and epicardial coronary arteries and veins. CAV is characterized by vascular injury induced by a variety of noxious stimuli, including the immune system response to the allograft, ischemia-reperfusion injury, viral infection, immunosuppressive drugs, and classic risk factors such as hyperlipidemia, **insulin resistance**, and **hypertension**. The obstructive vascular lesions are thought to progress through repetitive endothelial injury followed by repair response. The role of major histocompatibility complex **donor** -recipient differences in the pathogenesis of CAV has not yet been completely elucidated. Intracoronary ultrasound studies reveal a dual morphology with **donor**-transmitted or de novo focal, noncircumferential plaques in proximal segments and/or a diffuse, concentric pattern observed in distal segments. A lack of correlation between microvascular and epicardial vessel disease suggests discordant manifestations and progression of CAV. Apoptosis and loss of functional vascular remodeling have to be considered as important mediators of clinically relevant CAV. Strategies for blocking T-cell costimulation and expression of adhesion molecules may help prevent chronic rejection in clinical transplantation. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and antiproliferative drugs may slow progression of CAV by various effects. Methods to augment endogenous **nitric oxide** bioavailability as well as newer immunosuppressive regimens may be protective. Balloon angioplasty has a limited role in the treatment of focal lesions. Experiences with coronary stenting, coronary artery bypass grafting, and transmyocardial laser revascularization are limited. Retransplantation has a worse outcome than initial transplantation.

ACCESSION NUMBER: 1997:449867 BIOSIS
DOCUMENT NUMBER: PREV199799749070
TITLE: Cardiac allograft vasculopathy: A review.
AUTHOR(S): Weiss, Michael [Reprint author]; Von Scheidt, Wolfgang
CORPORATE SOURCE: Med. Klinik Poliklinik I, Klinikum Grosshadern, Univ. Munich, Marchioninistr. 15, 81377 Munich, Germany
SOURCE: Circulation, (1997) Vol. 96, No. 6, pp. 2069-2077. CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Oct 1997
Last Updated on STN: 27 Oct 1997
SO Circulation, (1997) Vol. 96, No. 6, pp. 2069-2077.
CODEN: CIRCAZ. ISSN: 0009-7322.
AB. . . the immune system response to the allograft, ischemia-reperfusion injury, viral infection, immunosuppressive drugs, and classic risk factors such as hyperlipidemia, **insulin resistance**, and **hypertension**. The obstructive vascular lesions are thought to progress through repetitive endothelial injury followed by repair response. The role of major histocompatibility complex **donor** -recipient differences in the pathogenesis of CAV has not yet been completely elucidated. Intracoronary ultrasound studies reveal a dual morphology with **donor**-transmitted or de novo focal, noncircumferential plaques in proximal segments and/or a diffuse, concentric pattern observed in distal segments. A lack. . . 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and antiproliferative drugs may slow progression of CAV by various effects. Methods to augment endogenous **nitric oxide** bioavailability as well as newer immunosuppressive regimens may be protective. Balloon angioplasty has a limited role in the treatment of. . .

L6 ANSWER 8 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AB Objectives. We sought to determine whether hypertriglyceridemia in patients with lipoprotein lipase (LPL) dysfunction is associated with endothelial dysfunction in **resistance** vessels of the forearm vasculature. Background. Vasodilator responses to acetylcholine, acting through stimulation of **nitric oxide** (NO) release from the endothelium, are impaired in hypercholesterolemia and normalized by L-arginine, suggesting dysfunction of the L-arginine/NO pathway. Similar abnormalities have been reported in conditions associated with hypertriglyceridemia, such as non-**insulin**-dependent **diabetes**. The relation between endothelial function and plasma triglyceride concentrations has, however, not previously been studied in vivo. Methods. We examined forearm blood flow responses to brachial artery infusions of acetylcholine (alone and with L-arginine) and nitroprusside (an NO **donor**) in 17 patients with severe hypertriglyceridemia (mean (+-SD) plasma triglyceride concentration 1,914 +- 1,288 mg/dl) but normal low density lipoprotein cholesterol (89 +- 31 mg/di) and in 34 normolipidemic control subjects. Severe LPL dysfunction was demonstrated in 10 of 17 patients. Results. Acetylcholine (7.5 and 15 mu-g/min) produced similar forearm blood flow responses in hypertriglyceridemic patients (mean (+- SEM) 7.7 +- 0.9 and 10.5 +- 1.2 ml/min per 100 ml) and in control subjects (7.5 +- 0.6 and 11.0 +- 0.8 ml/min per 100 ml, p = 0.78 by analysis of variance). Responses to acetylcholine co-infused With L-arginine (10 mg/min) and nitroprusside (3 and 10 mu-g/min) were also similar in hypertriglyceridemic patients and control subjects (p = 0.93 and p = 0.27 for acetylcholine with L-arginine

and nitroprusside, respectively). The ratio response to acetylcholine/response to nitroprusside differed between hypertriglyceridemic patients and control subjects by only 1%. The study had gt 90% power (alpha = 0.05) to detect a difference gt 30% in this ratio. Conclusions. Severe hypertriglyceridemia associated with LPL dysfunction is not associated with the degree of endothelial dysfunction seen in moderate hypercholesterolemia when responses to acetylcholine are impaired by gt 40%.

ACCESSION NUMBER: 1997:213595 BIOSIS
DOCUMENT NUMBER: PREV199799520099
TITLE: Preserved endothelial function in patients with severe hypertriglyceridemia and low functional lipoprotein lipase activity.
AUTHOR(S): Chowienczyk, Philip J. [Reprint author]; Watts, Gerald F.; Wierzbicki, Anthony S.; Cockcroft, John R.; Brett, Sally E.; Ritter, James M.
CORPORATE SOURCE: Dep. Clinical Pharmacol., St. Thomas' Hosp., Lambeth Palace Rd., London SE1 7EH, UK
SOURCE: Journal of the American College of Cardiology, (1997) Vol. 29, No. 5, pp. 964-968.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 May 1997
Last Updated on STN: 22 May 1997

SO Journal of the American College of Cardiology, (1997) Vol. 29, No. 5, pp. 964-968.
CODEN: JACCDI. ISSN: 0735-1097.

AB. . . Objectives. We sought to determine whether hypertriglyceridemia in patients with lipoprotein lipase (LPL) dysfunction is associated with endothelial dysfunction in **resistance** vessels of the forearm vasculature. Background. Vasodilator responses to acetylcholine, acting through stimulation of **nitric oxide** (NO) release from the endothelium, are impaired in hypercholesterolemia and normalized by L-arginine, suggesting dysfunction of the L-arginine/NO pathway. Similar abnormalities have been reported in conditions associated with hypertriglyceridemia, such as non-**insulin**-dependent **diabetes**. The relation between endothelial function and plasma triglyceride concentrations has, however, not previously been studied in vivo. Methods. We examined forearm blood flow responses to brachial artery infusions of acetylcholine (alone and with L-arginine) and nitroprusside (an NO **donor**) in 17 patients with severe hypertriglyceridemia (mean (+-SD) plasma triglyceride concentration 1,914 +- 1,288 mg/dl) but normal low density lipoprotein. . .

IT . . .
CARDIOVASCULAR MEDICINE; ENDOTHELIAL DYSFUNCTION; FOREARM BLOOD FLOW; HYPERTRIGLYCERIDEMIA; LIPOPROTEIN LIPASE DYSFUNCTION; LOW-DENSITY LIPOPROTEIN CHOLESTEROL; METABOLIC DISEASE; METABOLISM; NITRIC OXIDE; NON-INSULIN-DEPENDENT **DIABETES**; PATIENT; PLASMA CONCENTRATIONS; TRIGLYCERIDE; VASCULAR DISEASE

L6 ANSWER 9 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AB The effect of **insulin** on Na+ pump activity, measured as ouabain-**sensitive** (OS) 86Rb uptake, was studied in the rabbit aorta. In the absence of **insulin**, incubation of endothelium-intact rings for 3 h in a medium containing a high concentration of glucose (44 mM) decreased OS 86Rb uptake by 42% compared with that observed at 5.5 mM glucose. Addition of **insulin** (0.1-10 mU/ml) increased OS 86Rb uptake at both glucose concentrations and eliminated the differences

between the groups. **Insulin** also increased OS 86Rb uptake in endothelium-intact and -denuded (ED) rings in the presence of the **nitric oxide** (NO) synthase inhibitor N-G-monomethyl-L-arginine. Removal of the endothelium before the incubations did not diminish the **insulin**-induced increase in OS 86Rb uptake, which was concentration dependent. The NO **donor** sodium nitroprusside increased OS 86Rb uptake in ED rings, and its effect and that of **insulin** were additive. Phorbol 12,13-dibutyrate, a direct activator of protein kinase C (PKC), also increased OS 86Rb uptake in ED rings; however, its effect and that of **insulin** were not additive. The PKC inhibitor bisindolylmaleimide totally inhibited **insulin**-induced, but not sodium nitroprusside-induced, increases in OS 86Rb uptake. The results suggest that **insulin** activates the Na+ pump in the aorta and reverses the inhibition of the pump caused by hyperglycemia. This effect of **insulin** can occur at physiological concentrations, is independent of endothelium-derived NO, and is presumably mediated by an increase in PKC activity. In contrast, activation of the Na+ pump by NO appears to be independent of PKC.

ACCESSION NUMBER: 1996:264246 BIOSIS
DOCUMENT NUMBER: PREV199698820375
TITLE: Differential stimulation of Na+ pump activity by insulin and nitric oxide in rabbit aorta.
AUTHOR(S): Gupta, Sandeep [Reprint author]; Phipps, Krista; Ruderman, Neil B.
CORPORATE SOURCE: Dep. Urol., CABR, W607, 700 Albany St., Boston Univ. Sch. Medicine, Boston, MA 02118, USA
SOURCE: American Journal of Physiology, (1996) Vol. 270, No. 4 PART 2, pp. H1287-H1293.
CODEN: AJPHAP. ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Jun 1996
Last Updated on STN: 10 Jun 1996
SO American Journal of Physiology, (1996) Vol. 270, No. 4 PART 2, pp. H1287-H1293.
CODEN: AJPHAP. ISSN: 0002-9513.
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and is presumably mediated by an increase in PKC activity.. . .

IT Miscellaneous Descriptors
CYCLIC GMP; **DIABETES**; PROTEIN KINASE C; RUBIDIUM-86 UPTAKE; SODIUM-POTASSIUM ATPASE; VASCULAR FUNCTION

L6 ANSWER 10 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB Objectives: This study sought to determine whether **nitric oxide**-mediated vasodilation is abnormal in patients with noninsulin-dependent **diabetes** mellitus. Background: Multiple investigations, both in experimental models and in patients with **insulin**-dependent **diabetes** mellitus, demonstrate impaired endothelium-dependent vasodilation. Decreased availability of endothelium-derived **nitric oxide** may contribute to the high prevalence of vascular disease in **diabetes**. Methods: Vascular reactivity was measured in the forearm **resistance** vessels of 21 patients with non-**insulin**-dependent **diabetes** mellitus and 23 matched healthy control subjects. No patient had **hypertension** or hypercholesterolemia. Each subject was pretreated with aspirin to inhibit endogenous production of vasoactive prostanoids. Methacholine chloride (0.3 to 10 mu-g/min) was administered through a brachial artery cannula to assess vasodilation to endothelium-derived **nitric oxide**. Sodium nitroprusside (0.3 to 10 mu-g/min) was infused to evaluate vasodilation to an exogenous **nitric oxide donor**. Verapamil (10 to 300 mu-g/min) was administered to distinguish impaired **nitric oxide**-mediated vasodilation from general dysfunction of vascular smooth muscle. Forearm blood flow was determined by venous occlusion plethysmography, and dose-response curves were generated for each agent. To assess the role of vasoconstrictor prostanoids, a subset of eight **diabetic** subjects were reexamined in the absence of aspirin treatment. Results: Basal forearm blood flow in **diabetic** and nondiabetic subjects was comparable. The forearm blood flow responses to both methacholine chloride and nitroprusside were significantly attenuated in **diabetic** compared with nondiabetic subjects (p lt 0.005 by analysis of variance for both agents). In contrast, the response to verapamil was not significantly different between the groups (p gt 0.50). The forearm blood flow responses to these agents were not significantly affected by cyclooxygenase inhibition. Conclusions: **Nitric oxide**-mediated vasodilation is impaired in non-**insulin**-dependent **diabetes** mellitus. Vasoconstrictor prostanoids do not contribute significantly to vascular dysfunction. The attenuated response to exogenous as well as endogenous **nitric oxide donors** suggests that the abnormality is due to increased inactivation of **nitric oxide** or to decreased reactivity of the vascular smooth muscle to **nitric oxide**.

ACCESSION NUMBER: 1996:183569 BIOSIS
DOCUMENT NUMBER: PREV199698739698
TITLE: Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent **diabetes** mellitus.
AUTHOR(S): Williams, Stephen B.; Cusco, Jorge A.; Roddy, Mary-Anne; Johnstone, Michael T.; Creager, Mark A. [Reprint author]
CORPORATE SOURCE: Cardiovasc. Div., Brigham Women's Hosp., 75 Francis St., Boston, MA 02215, USA
SOURCE: Journal of the American College of Cardiology, (1996) Vol. 27, No. 3, pp. 567-574.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Article
LANGUAGE: English

ENTRY DATE: Entered STN: 29 Apr 1996
Last Updated on STN: 29 Apr 1996

TI Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent **diabetes** mellitus.

SO Journal of the American College of Cardiology, (1996) Vol. 27, No. 3, pp. 567-574.
CODEN: JACCDI. ISSN: 0735-1097.

AB Objectives: This study sought to determine whether **nitric oxide**-mediated vasodilation is abnormal in patients with noninsulin-dependent **diabetes** mellitus. Background: Multiple investigations, both in experimental models and in patients with **insulin**-dependent **diabetes** mellitus, demonstrate impaired endothelium-dependent vasodilation. Decreased availability of endothelium-derived **nitric oxide** may contribute to the high prevalence of vascular disease in **diabetes**. Methods: Vascular reactivity was measured in the forearm **resistance** vessels of 21 patients with non-**insulin**-dependent **diabetes** mellitus and 23 matched healthy control subjects. No patient had **hypertension** or hypercholesterolemia. Each subject was pretreated with aspirin to inhibit endogenous production of vasoactive prostanoids. Methacholine chloride (0.3 to 10 mu-g/min) was administered through a brachial artery cannula to assess vasodilation to endothelium-derived **nitric oxide**. Sodium nitroprusside (0.3 to 10 mu-g/min) was infused to evaluate vasodilation to an exogenous **nitric oxide donor**. Verapamil (10 to 300 mu-g/min) was administered to distinguish impaired **nitric oxide**-mediated vasodilation from general dysfunction of vascular smooth muscle. Forearm blood flow was determined by venous occlusion plethysmography, and dose-response curves were generated for each agent. To assess the role of vasoconstrictor prostanoids, a subset of eight **diabetic** subjects were reexamined in the absence of aspirin treatment. Results: Basal forearm blood flow in **diabetic** and nondiabetic subjects was comparable. The forearm blood flow responses to both methacholine chloride and nitroprusside were significantly attenuated in **diabetic** compared with nondiabetic subjects (p lt 0.005 by analysis of variance for both agents). In contrast, the response to verapamil. . . groups (p gt 0.50). The forearm blood flow responses to these agents were not significantly affected by cyclooxygenase inhibition. Conclusions: **Nitric oxide**-mediated vasodilation is impaired in non-**insulin** -dependent **diabetes** mellitus. Vasoconstrictor prostanoids do not contribute significantly to vascular dysfunction. The attenuated response to exogenous as well as endogenous **nitric oxide donors** suggests that the abnormality is due to increased inactivation of **nitric oxide** or to decreased reactivity of the vascular smooth muscle to **nitric oxide** .

L6 ANSWER 11 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB Desmopressin (DDAVP), an AVP cntdot V-2-receptor **agonist**, evokes endothelium-dependent relaxation (EDR) due to **nitric oxide** (NO), EDR factor (EDRF) in the systemic vasculature, and glomerular afferent arterioles via AVP receptor(s). Glyceryl trinitrate (GTN) causes endothelium-independent (nonreceptor-mediated) vasodilation. We elucidated the possible involvement of EDRF in early non-**insulin**-dependent **diabetes** mellitus (NIDDM) and glomerular hyperfiltration (GHF) by DDAVP and GTN infusions. Patients with advanced DM nephropathy (DM cntdot Np) (n = 7) were also examined. DDAVP and GTN decreased the mean blood pressure in DM with GHF (DM + GHF)

and without GHF (DM-GHF) greater than that in normal subjects (N), without any difference in the heart rate changes in any group. Plasma levels of cGMP, a cellular messenger of NO, were significantly increased by DDAVP and GTN with a similar increment in each group. DDAVP caused a significant increase in urinary cGMP excretion in each group with a similar increment in each group. However, it caused a transient increase in creatinine clearance only in DM + GHF although GTN did not, and an exaggerated excretion of urinary albumin in early NIDDM, especially in DM + GHF, without a change in beta-2-microglobulin excretion. In contrast, in DM cntdot Np GTN caused a decrease in blood pressure and an increase in plasma cGMP levels, but DDAVP did not. In conclusion, in peripheral vasculature and kidney, an enhanced **sensitivity** of vascular smooth muscle to NO is present in early NIDDM. The exaggerated dilation of glomerular afferent arterioles by preferentially produced NO in in situ, which causes a rise in P-GC, might be partly responsible for the glomerular hyperfiltration and subsequently the increase in the glomerular protein permeation of DM + GHF. However, in peripheral blood vessels of DM cntdot N-p EDR is impaired. Thus, EDR seems to change with the development of NIDDM.

ACCESSION NUMBER: 1995:544526 BIOSIS
DOCUMENT NUMBER: PREV199698558826
TITLE: Endothelium-dependent relaxation in peripheral vasculature and kidney of non-insulin-dependent **diabetes** mellitus.
AUTHOR(S): Yamada, Kenichi [Reprint author]; Nakano, Hirofumi; Nakayama, Masaaki; Nozaki, Osamu; Miura, Yasuhiko; Nishimura, Notonobu; Tsuchida, Hiroki; Mimura, Nobuhide
CORPORATE SOURCE: Div. Clinical Res. Intern. Med., Sakura Natl. Hosp., 2-36-2 Ebaradai, Sakura, Chiba 285, Japan
SOURCE: Journal of Diabetes and its Complications, (1995) Vol. 9, No. 4, pp. 203-207.
ISSN: 1056-8727.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 1995
Last Updated on STN: 31 Dec 1995

TI Endothelium-dependent relaxation in peripheral vasculature and kidney of non-insulin-dependent **diabetes** mellitus.
SO Journal of Diabetes and its Complications, (1995) Vol. 9, No. 4, pp. 203-207.
ISSN: 1056-8727.
AB Desmopressin (DDAVP), an AVP cntdot V-2-receptor **agonist**, evokes endothelium-dependent relaxation (EDR) due to **nitric oxide** (NO), EDR factor (EDRF) in the systemic vasculature, and glomerular afferent arterioles via AVP receptor(s). Glyceryl trinitrate (GTN) causes endothelium-independent (nonreceptor-mediated) vasodilation. We elucidated the possible involvement of EDRF in early non-**insulin**-dependent **diabetes** mellitus (NIDDM) and glomerular hyperfiltration (GHF) by DDAVP and GTN infusions. Patients with advanced DM nephropathy (DM cntdot Np) (n. . . and an increase in plasma cGMP levels, but DDAVP did not. In conclusion, in peripheral vasculature and kidney, an enhanced **sensitivity** of vascular smooth muscle to NO is present in early NIDDM. The exaggerated dilation of glomerular afferent arterioles by preferentially. . .
IT Miscellaneous Descriptors
CYCLIC GMP; DESMOPRESSIN; **DIABETIC** NEPHROPATHY; GLOMERULAR HYPERFILTRATION; GLYCERYL TRINITRATE; NITRIC OXIDE; URINARY ALBUMIN

L6 ANSWER 12 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB The ability of beta cells to endure assaults may be relevant in the development of **insulin**-dependent **diabetes** mellitus. This study examines the susceptibility of human pancreatic islets to agents that are cytotoxic for rodent beta cells - i.e., sodium nitroprusside (NP, a **nitric oxide donor**), streptozotocin (SZ), or alloxan. After 5-8 days in tissue culture, human or rodent islets were exposed for 14 h to NP (50-200 mu-M) or for 30 min to SZ or alloxan (1-3 mM). Glucose oxidation by human islets was not reduced by NP, but there was a dose-dependent inhibition in rat (40-90% inhibition; P lt 0.001) and mouse (10-60% inhibition; P lt 0.05) islet glucose oxidation. Glucose (16.7 mM)-induced **insulin** release by human islets was not impaired after a 30-min exposure to SZ or alloxan, at concentrations that inhibited **insulin** release from rat (30-80% inhibition; P lt 0.001) or mouse (10-70% inhibition; P lt 0.05) islets. The viability of human beta cells purified by flow cytometry was not affected by SZ or alloxan (5 mM), as judged 1 or 4 days after a 10-min exposure and subsequent culture; these conditions were cytotoxic for rat beta cells, with 65-95% (P lt 0.01) dead beta cells after 4 days. Human islets transplanted under the kidney capsule of nude mice were not affected by in vivo alloxan exposure, as suggested by preserved graft morphology and **insulin** content, whereas the endogenous beta cells of the transplanted mice were severely damaged (80% decrease in pancreatic **insulin** content and morphological signs of beta-cell destruction). Thus human beta cells are **resistant** to NP, SZ, or alloxan at concentrations that decrease survival and function of rat or mouse beta cells. These marked interspecies differences emphasize the relevance of repair and/or defense mechanisms in beta-cell destruction and raise the possibility that such differences may also be present among individuals of the same species.

ACCESSION NUMBER: 1994:497531 BIOSIS
DOCUMENT NUMBER: PREV199497510531
TITLE: Major species differences between humans and rodents in the susceptibility to pancreatic beta-cell injury.
AUTHOR(S): Eizirik, Decio L. [Reprint author]; Pipeleers, Daniel G.; Ling, Zhidong; Welsh, Nils; Hellerstrom, Claes; Andersson, Arne
CORPORATE SOURCE: Dep. Med. Cell Biol., Uppsala University, Biomedicum, P.O. Box 571, S-751 23 Uppsala, Sweden
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 20, pp. 9253-9256.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Nov 1994
Last Updated on STN: 29 Nov 1994

SO Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 20, pp. 9253-9256.
CODEN: PNASA6. ISSN: 0027-8424.
AB The ability of beta cells to endure assaults may be relevant in the development of **insulin**-dependent **diabetes** mellitus. This study examines the susceptibility of human pancreatic islets to agents that are cytotoxic for rodent beta cells - i.e., sodium nitroprusside (NP, a **nitric oxide donor**), streptozotocin (SZ), or alloxan. After 5-8 days in tissue culture, human or rodent islets were exposed for 14 h to. . . in rat (40-90% inhibition; P lt 0.001) and mouse (10-60% inhibition; P lt 0.05) islet glucose oxidation. Glucose (16.7 mM)-induced **insulin** release by human islets was not impaired after a 30-min exposure to SZ or alloxan, at

concentrations that inhibited **insulin** release from rat (30-80% inhibition; P lt 0.001) or mouse (10-70% inhibition; P lt 0.05) islets. The viability of human. . . kidney capsule of nude mice were not affected by in vivo alloxan exposure, as suggested by preserved graft morphology and **insulin** content, whereas the endogenous beta cells of the transplanted mice were severely damaged (80% decrease in pancreatic **insulin** content and morphological signs of beta-cell destruction). Thus human beta cells are **resistant** to NP, SZ, or alloxan at concentrations that decrease survival and function of rat or mouse beta cells. These marked. . .

IT Miscellaneous Descriptors
ALLOXAN; **DIABETOGEN**; INSULIN-DEPENDENT **DIABETES** MELLITUS; NITRIC OXIDE; SODIUM NITROPRUSSIDE; STREPTOZOTOCIN

L6 ANSWER 13 OF 26 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AB To compare the **sensitivity** of different mammalian cell types towards the cytotoxic action of **nitric oxide**, freshly isolated rat pancreatic islet cells, hepatocytes, resident and activated macrophages, cultured aortic endothelial cells and two murine tumor cell lines were tested for susceptibility towards exogenous **nitric oxide**. As sources for **nitric oxide** nitroprusside, S-nitroso-N-acetyl-penicillamine and the sydnonimine-derivative SIN-1 were used. These generate **nitric oxide** by different mechanisms and kinetics. Among the cell types tested we found large differences in their susceptibility towards the three **nitric oxide donors**. Islet cells were by far the most **sensitive** of the investigated cells and were completely lysed by all three **nitric oxide donors**. Hepatocytes and endothelial cells were **sensitive** towards nitroprusside but relatively **resistant** towards toxicity of SIN-1 and S-nitroso-N-acetyl-penicillamine. Activated and resident macrophages were lysed by SIN-1, whereas high concentrations of nitroprusside and S-nitroso-N-acetyl-penicillamine led to partial cell lysis only. The tumor cell lines were both lysed by SIN-1 but showed differences in their **sensitivity** towards S-nitroso-N-acetyl-penicillamine. **Nitric oxide**, which is produced in large amounts during infection and inflammation, may play an important role in the destruction of islet cells during insulitis leading to **insulin**-dependent **diabetes** mellitus.

ACCESSION NUMBER: 1993:476965 BIOSIS
DOCUMENT NUMBER: PREV199396110565
TITLE: Pancreatic islet cells are highly susceptible towards the cytotoxic effects of chemically generated nitric oxide.
AUTHOR(S): Kroencke, Klaus-D.; Brenner, Heinz-H.; Rodriguez, Maria-L.; Etzkorn, Kai; Noack, Eike A.; Kolb, Hubert; Kolb-Bachofen, Victoria [Reprint author]
CORPORATE SOURCE: Inst. Immunobiol., Dep. Med., Heinrich-Heine-Univ. Duesseldorf, Moorenstr. 5, D-4000 Duesseldorf 1, Germany
SOURCE: Biochimica et Biophysica Acta, (1993) Vol. 1182, No. 2, pp. 221-229.
CODEN: BBACAQ. ISSN: 0006-3002.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Oct 1993
Last Updated on STN: 23 Oct 1993

SO Biochimica et Biophysica Acta, (1993) Vol. 1182, No. 2, pp. 221-229.
CODEN: BBACAQ. ISSN: 0006-3002.

AB To compare the **sensitivity** of different mammalian cell types towards the cytotoxic action of **nitric oxide**, freshly

isolated rat pancreatic islet cells, hepatocytes, resident and activated macrophages, cultured aortic endothelial cells and two murine tumor cell lines were tested for susceptibility towards exogenous **nitric oxide**. As sources for **nitric oxide** nitroprusside, S-nitroso-N-acetyl-penicillamine and the sydnonimine-derivative SIN-1 were used. These generate **nitric oxide** by different mechanisms and kinetics. Among the cell types tested we found large differences in their susceptibility towards the three **nitric oxide donors**. Islet cells were by far the most **sensitive** of the investigated cells and were completely lysed by all three **nitric oxide donors**. Hepatocytes and endothelial cells were **sensitive** towards nitroprusside but relatively **resistant** towards toxicity of SIN-1 and S-nitroso-N-acetyl-penicillamine. Activated and resident macrophages were lysed by SIN-1, whereas high concentrations of nitroprusside and. . . led to partial cell lysis only. The tumor cell lines were both lysed by SIN-1 but showed differences in their **sensitivity** towards S-nitroso-N-acetyl-penicillamine. **Nitric oxide**, which is produced in large amounts during infection and inflammation, may play an important role in the destruction of islet cells during insulitis leading to **insulin**-dependent **diabetes** mellitus.

L6 ANSWER 14 OF 26 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 1998:28030398 BIOTECHNO
AB OBJECTIVE - Previous studies in our laboratory showed that the platelet anti-aggregating effect exerted by **insulin**, mediated by a **nitric oxide** (NO)- induced increase of guanosine-3',5'-cyclic monophosphate (cGMP), is lost in the **insulin-resistant** states of **obesity** and **obese** NIDDM. It is not clear 1) whether the alterations observed in **obese** NIDDM patients are attributable to the **obesity** -related **insulin resistance** or to **diabetes** per se and 2) whether **insulin-resistant** states present a normal or a blunted response to NO. This study has been conducted to investigate 1) the platelet **sensitivity** to **insulin** in lean NIDDM and 2) the platelet **sensitivity** to an NO **donor**, glyceryl trinitrate (GTN), in **obesity** and in both lean and **obese** NIDDM. RESEARCH DESIGN AND METHODS - We determined 1) ADP-induced platelet aggregation and platelet cGMP content in platelet-rich plasma (PRP) obtained from 11 lean NIDDM patients, after a 3-min incubation with **insulin** (0, 240, 480, 960, 1,920 pmol/1) and 2) ADP-induced platelet aggregation and platelet cGMP content in PRP obtained from 9 **obese** subjects, 11 lean and 8 **obese** NIDDM patients, and 18 control subjects, after a 3-min incubation with 0, 20, 40, and 100 μmol/l GTN. RESULTS - **Insulin** dose-dependently decreased platelet aggregation in lean NIDDM patients (P = 0.0001): with 1,920 pmol/l of **insulin**, ADP ED.sub.5.sub.0 was 141.5 ± 6.4% of basal values (P = 0.0001). Furthermore, **insulin** increased platelet cGMP (P = 0.0001) from 7.5 ± 0.2 to 21.1 ± 3.7 pmol/10.sup.9 platelets. These results were similar to those previously described in healthy subjects. GTN reduced platelet aggregation in all the groups (P = 0.0001) at all the concentrations tested (P = 0.0001), but GTN IC.sub.5.sub.0 values were much higher in **insulin-resistant** patients: 36.3 ± 5.0 μmol/l in healthy control subjects, 26.0 ± 6.0 μmol/l in lean NIDDM patients (NS vs. control subjects), 123.6 ± 24.0 μmol/l in **obese** subjects (P = 0.0001 vs. control subjects), and 110.1 ± 19.2 μmol/l in **obese** NIDDM patients (P = 0.0001 vs.

control subjects). GTN dose-dependently increased platelet cGMP in all the groups (P = 0.0001 in control subjects, lean NIDDM patients, and **obese** subjects; P = 0.04 in **obese** NIDDM patients). Values reached by **obese** subjects and **obese** NIDDM patients, however, were lower than those reached by control subjects (with 100 μmol/l of GTN, P = 0.001 and P = 0.0001, respectively). In healthy control subjects and in **obese** subjects, the **insulin**:glucose ratio, used as an indirect measure of **insulin sensitivity**, was positively correlated to GTN IC.sub.5.sub.0 (r = 0.530, P = 0.008), further suggesting that the **sensitivity** to NO is reduced in the presence of **insulin resistance**. CONCLUSIONS - The **insulin** anti-aggregating effect is preserved in lean NIDDM; platelet **sensitivity** to GTN is preserved in lean NIDDM but is reduced in the **insulin**-**resistant** states of **obesity** and **obese** NIDDM. **Resistance** to nitrates, therefore, could be considered another feature of the **insulin-resistance** syndrome.

ACCESSION NUMBER: 1998:28030398 BIOTECHNO
TITLE: Platelet **resistance** to nitrates in **obesity** and **obese** NIDDM, and normal platelet **sensitivity** to both **insulin** and nitrates in lean NIDDM
AUTHOR: Anfossi G.; Mularoni E.M.; Burzacca S.; Ponziani M.C.; Massucco P.; Mattiello L.; Cavalot F.; Trovati M.
CORPORATE SOURCE: Dr. M. Trovati, Diabetes Unit, Dept. of Clinic. and Biological Sci., University of Turin, 10043 Orbassano (Turin), Italy.
SOURCE: Diabetes Care, (**1998**), 21/1 (121-126), 37 reference(s)
CODEN: DICAD2 ISSN: 0149-5992
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Platelet **resistance** to nitrates in **obesity** and **obese** NIDDM, and normal platelet **sensitivity** to both **insulin** and nitrates in lean NIDDM

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CT *__insulin__; *nitrate; *glyceryl trinitrate; *recombinant human **insulin**; *non **insulin** dependent **diabetes** mellitus; ***diabetic obesity**; ***insulin resistance**; **nitric oxide donor**; cyclic gmp; **nitric oxide**; glucose; thrombocyte aggregation; **obesity**; **insulin sensitivity**; thrombogenesis; drug mechanism; human; male; female; clinical article; controlled study; adult; article

RN (**insulin**) 9004-10-8; (nitrate) 14797-55-8; (glyceryl trinitrate) 55-63-0; (cyclic GMP) 7665-99-8; (**nitric oxide**) 10102-43-9; (glucose) 50-99-7, 84778-64-3

L6 ANSWER 15 OF 26 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN

AN 1993:23267046 BIOTECHNO

AB To compare the **sensitivity** of different mammalian cell types towards the cytotoxic action of **nitric oxide**, freshly isolated rat pancreatic islet cells, hepatocytes, resident and activated macrophages, cultured aortic endothelial cells and two murine tumor cell lines were tested for susceptibility towards exogenous **nitric oxide**. As source for **nitric oxide** nitroprusside, S-nitroso-N-acetyl-penicillamine and the sydnonimine-derivative SIN-1 were used. These generate **nitric oxide** by different mechanisms and kinetics. Among the cell types tested we found large differences in their susceptibility towards the three **nitric oxide donors**. Islet cells were by far the most **sensitive** of the investigated cells and were completely lysed by all three **nitric oxide donors**. Hepatocytes and endothelial cells were **sensitive** towards nitroprusside but relatively **resistant** towards toxicity

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ACCESSION NUMBER: 1993:23267046 BIOTECHNO
TITLE: Pancreatic islet cells are highly susceptible towards the cytotoxic effects of chemically generated **nitric oxide**
AUTHOR: Kroncke K.-D.; Brenner H.-H.; Rodriguez M.-L.; Etzkorn K.; Noack E.A.; Kolb H.; Kolb-Bachofen V.
CORPORATE SOURCE: Institute of Immunobiology, Department of Medicine, Heinrich-Heine-Univ. Dusseldorf, Moorenstrasse 5,D-4000 Dusseldorf 1, Germany.
SOURCE: Biochimica et Biophysica Acta - Molecular Basis of Disease, (**1993**), 1182/2 (221-229)
CODEN: BBADEX ISSN: 0925-4439
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Pancreatic islet cells are highly susceptible towards the cytotoxic effects of chemically generated **nitric oxide**

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CODEN: BBADEX ISSN: 0925-4439

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CT *linsidomine; *n acetyl s nitrosopenicillamine; ***nitric oxide**; *nitroprusside sodium; *cytotoxicity; *pancreas islet cell; animal cell; article; cell type; controlled study; macrophage; mouse; nonhuman; priority journal; rat; tumor. . .

RN (linsidomine) 16142-27-1, 33876-97-0; (n acetyl s nitrosopenicillamine)

79032-48-7; (**nitric oxide**) 10102-43-9; (nitroprusside sodium) 14402-89-2, 15078-28-1

L6 ANSWER 16 OF 26 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 1993:23073063 BIOTECHNO
AB The aim of the present study was to characterize the effects of human recombinant interleukin-1β (rIL-1β) on human pancreatic islets. For this purpose, islets isolated from adult cadaveric **donors** were exposed to rIL-1β (1 or 3 ng/mL) for different periods of time. In some experiments, rat pancreatic islets were exposed in parallel to the cytokine. After 48 h of culture in the presence of rIL-1β, the human islets showed an increased **insulin** release during short term incubations in the presence of 1.7 or 16.7 mM glucose. There was also a 3- to 4-fold increase in **insulin** accumulation into the culture medium, but rIL-1β did not affect human islet glucose metabolism. These stimulatory effects of rIL-1β on human islets were already present after an acute (2-h) exposure to the cytokine, and this functional stimulation was blocked by an IL-1 receptor antagonist protein. After exposure of human islets to rIL-1β for 6 days, there was no effect of the cytokine on either glucose metabolism or **insulin** release compared to those in control islets. Rat islets exposed for 48 h in culture to the same concentrations of rIL-1β, however, showed a 40-60% decrease in **insulin** accumulation into the medium, glucose-induced **insulin** release, and glucose oxidation. Moreover, while there was no effect of rIL-1β on nitrite production by human islets, there was a 7- to 11-fold increase in nitrite production by rat islets. Nitrite is an end product of the highly reactive radical **nitric oxide** (NO), and there are data to suggest that NO is an important mediator of the suppressive and cytotoxic actions of IL-1 on rat islets. The present observations suggest that human islets are less **sensitive** to the inhibitory effects of human rIL-1β than rat islets, and that this is due to a lack of induction of NO synthesis by the cytokine in human islet cells.
ACCESSION NUMBER: 1993:23073063 BIOTECHNO
TITLE: Predominance of stimulatory effects of interleukin-1β on isolated human pancreatic islets
AUTHOR: Eizirik D.L.; Welsh N.; Hellerstrom C.
CORPORATE SOURCE: Department of Medical Cell Biology, Uppsala University, Box 571,S-751 23 Uppsala, Sweden.
SOURCE: Journal of Clinical Endocrinology and Metabolism, (**1993**), 76/2 (399-403)
CODEN: JCEMAZ ISSN: 0021-972X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
SO Journal of Clinical Endocrinology and Metabolism, (**1993**), 76/2 (399-403)
CODEN: JCEMAZ ISSN: 0021-972X
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CT *dna; ***insulin***; ***nitric oxide***; *nitrite; *recombinant interleukin 1beta; *cell stimulation; *pancreas islet cell; **nitric oxide** synthase; animal cell; article; cytotoxicity; dna content; glucose oxidation; human; human cell; **insulin** dependent **diabetes** mellitus; **insulin** release; **insulin** synthesis; nonhuman; priority journal; rat

RN (dna) 9007-49-2; (**insulin**) 9004-10-8; (**nitric oxide**) 10102-43-9; (nitrite) 14797-65-0; (**nitric oxide** synthase) 125978-95-2

L6 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2004 ACS on STN

AB A review, with 52 refs. It is well documented that **insulin** has relevant vasoactive properties. In humans, systemic **insulin** infusion by the euglycemic clamp technique causes a dose-dependent increment in peripheral blood flow, suggesting a vasodilatory activity of the hormone. However **insulin** is not a direct relaxing compound since when it is directly injected into the brachial artery it does not increase forearm blood flow. Therefore it is conceivable that **insulin** acts as a modulator of vascular reactivity. Both in animals and humans **insulin** can attenuate the vasoconstrictor effect of adrenergic (noradrenaline, phenylephrine) and non-adrenergic (angiotensin II) mediators. Therefore it is now accepted that **insulin** blunts vasoconstriction by a non-specific mechanism. Moreover, **resistance** to this anti-vasoconstrictor effect of the hormone has been hypothesized as a possible mechanism responsible for **high blood-pressure** values associated with the **insulin resistance** states. Besides antagonizing vasoconstrictor stimuli, **insulin** also potentiates vascular relaxation, mainly when induced by endothelium-dependent **agonists** . In the forearm of normotensive subjects and essential **hypertensive** patients **insulin** potentiates the vasodilating effect of acetylcholine, an endothelium-dependent vasodilator. However, while in normotensive subjects the facilitating action of **insulin** on endothelium-dependent vasodilation is reversed by L-NMMA and therefore involves the **nitric oxide** pathway, in essential **hypertensive** patients it is caused by smooth muscle cell hyperpolarization. In summary, available evidence indicates that **insulin**-induced vasodilation is probably mediated by indirect mechanisms, including inhibition of contraction due to differrent stimuli and potentiation of endothelium-dependent relaxation. Whether all these vascular effects of **insulin** are relevant to metabolic and blood pressure homeostasis remains to be investigated.

ACCESSION NUMBER: 1997:408950 CAPLUS
DOCUMENT NUMBER: 127:76066
TITLE: Insulin and vascular reactivity
AUTHOR(S): Taddei, S.; Salvetti, A.
CORPORATE SOURCE: I Clinica Medica, University of Pisa, Pisa, 56100, Italy
SOURCE: Nutrition, Metabolism and Cardiovascular Diseases (**1997**), 7(2), 117-123
CODEN: NMCDEE; ISSN: 0939-4753
PUBLISHER: Medikal Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
SO Nutrition, Metabolism and Cardiovascular Diseases (**1997**), 7(2), 117-123
CODEN: NMCDEE; ISSN: 0939-4753
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L6 ANSWER 18 OF 26 CAPLUS COPYRIGHT 2004 ACS on STN
AB Considerable evidence has accumulated suggesting that cytokines, secreted from infiltrating immune cells, mediate the destruction of pancreatic islet B-cells seen in insulin-dependent **diabetes** mellitus. This action of cytokines results from intracellular generation of **nitric oxide** (NO) which is known to be cytotoxic to both rat and human isolated islets as well as to clonal B-cell lines. However, recent evidence suggests that, for reasons which remain unclear, human islets may be less susceptible than rodent pancreatic B-cells to NO-induced cytotoxicity. We have studied whether this is true for apoptosis, a cell death pathway which can be activated in rodent islets

and B-cell lines upon exposure to cytokines or chemical **nitric oxide donors**. We have used a range of apoptosis-inducing agents at high concns., over culture periods of 24-48h, and the results reveal that human islets are consistently less susceptible to induction of apoptosis than the rodent clonal B-cell lines, RINm5F and HIT-T15.

ACCESSION NUMBER: 1997:167798 CAPLUS
DOCUMENT NUMBER: 126:198020
TITLE: Human pancreatic islets display reduced sensitivity to nitric oxide-induced apoptosis compared to rodent clonal B-cell lines
AUTHOR(S): Loweth, A. C.; Williams, G. T.; Scarpello, J. H. B.; James, R. F. L.; Morgan, N. G.
CORPORATE SOURCE: Cellular Pharmacology Group, Departments of Biological Sciences and Medicine, Keele University, Staffordshire, ST5 5BG, UK
SOURCE: Diabetes Research (**1996**), 31(6), 231-241
CODEN: DIREEM; ISSN: 0265-5985
PUBLISHER: Teviot-Kimpton Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Diabetes Research (**1996**), 31(6), 231-241
CODEN: DIREEM; ISSN: 0265-5985

AB Considerable evidence has accumulated suggesting that cytokines, secreted from infiltrating immune cells, mediate the destruction of pancreatic islet B-cells seen in insulin-dependent **diabetes** mellitus. This action of cytokines results from intracellular generation of **nitric oxide** (NO) which is known to be cytotoxic to both rat and human isolated islets as well as to clonal B-cell lines. However, recent evidence suggests that, for reasons which remain unclear, human islets may be less susceptible than rodent pancreatic B-cells to NO-induced cytotoxicity. We have studied whether this is true for apoptosis, a cell death pathway which can be activated in rodent islets and B-cell lines upon exposure to cytokines or chemical **nitric oxide donors**. We have used a range of apoptosis-inducing agents at high concns., over culture periods of 24-48h, and the results reveal that human islets are consistently less susceptible to induction of apoptosis than the rodent clonal B-cell lines, RINm5F and HIT-T15.

IT **Diabetes** mellitus
(**insulin**-dependent; human pancreatic islets display reduced **sensitivity** to nitric oxide-induced apoptosis compared to rodent clonal B-cell lines)

L6 ANSWER 19 OF 26 CAPLUS COPYRIGHT 2004 ACS on STN

AB **Nitric oxide** (NO) has been proposed as a possible mediator of β-cell damage in human **insulin**-dependent **diabetes** mellitus (IDDM). This hypothesis is based on in vitro studies with rodent pancreatic islets. In the present study we examined whether human β-cells are affected by NO. In view of species differences in β-cell **sensitivity** to damaging agents, rat islets were investigated in parallel. Isolated islets were exposed for 90 min to different concns. of three chemical unrelated NO **donors**, 3-morpholino-sydnonimine (SIN-1), S-nitrosoglutathione (GSNO), or heptanitrosyltri-μ3-thioxotetraferrate(1-) (RBS). At the end of this incubation, human **insulin** release was mostly similar in control and NO-treated islets but, 48 h later, islet retrieval, islet DNA and **insulin** content, and glucose-induced **insulin** release were markedly lower in islets exposed to NO **donors**. Rat islets

were already inhibited during the initial 90 min; 48 h later their loss in β-cell function was similar to that in human islets. Nicotinamide or succinic acid monomethyl ester partially protected against SIN-1 induced islet cell loss, but not against the functional inhibition of human pancreatic islets. Exposure of human or rat islets to RBS was associated with significant DNA strand breakage, as judged by the comet assay (single cell gel electrophoresis) and by ultrastructural signs of cell damage. DNA damage was more severe in rat islet cells exposed to similar amts. of RBS. It is concluded that NO **donors** can damage human pancreatic islets, an effect paralleled by induction of nuclear DNA strand breaks.

ACCESSION NUMBER: 1996:280001 CAPLUS
DOCUMENT NUMBER: 125:7289
TITLE: **Nitric oxide donors** decrease the function and survival of human pancreatic islets
AUTHOR(S): Eizirik, D.ecio L.; Delaney, Carol A.; Green, Michael H. L.; Cunningham, James M.; Thorpe, Julian R.; Pipeleers, Daniel G.; Hellerstroem, Claes; Green, Irene C.
CORPORATE SOURCE: Department of Medical Cell Biology, Uppsala University, Biomedicum P.O. Box 571, Uppsala, S-751 23, Swed.
SOURCE: Molecular and Cellular Endocrinology (**1996**), 118(1,2), 71-83
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
TI **Nitric oxide donors** decrease the function and survival of human pancreatic islets
SO Molecular and Cellular Endocrinology (**1996**), 118(1,2), 71-83
CODEN: MCEND6; ISSN: 0303-7207
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ST **nitric oxide donor** pancreas **diabetes**
IT Deoxyribonucleic acids
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)

(damage, **nitric oxide donors** decrease function and survival of human pancreatic islets)
IT **Diabetes** mellitus
(insulin-dependent, **nitric oxide donors** decrease function and survival of human pancreatic islets)
IT Pancreatic islet of Langerhans
(β-cell, **nitric oxide donors** decrease function and survival of human pancreatic islets)
IT 98-92-0, Nicotinamide 3878-55-5, Succinic acid monomethyl ester
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nicotinamide effect on **nitric oxide donor** -induced decrease in function and survival of human pancreatic islets)
IT 12518-87-5, Heptanitrosyltri(sulfido)tetraferrate(1-) 33876-97-0, 3-Morpholino-sydnonimine 57564-91-7, S-Nitrosoglutathione
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**nitric oxide donors** decrease function and survival of human pancreatic islets)
IT 10102-43-9, **Nitric oxide**, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nitric oxide donors** decrease function and survival of human pancreatic islets)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release; **nitric oxide donors** decrease function and survival of human pancreatic islets)

L6 ANSWER 20 OF 26 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1998-45320 DRUGU P
AB Constipation is common among people with non-**insulin**-dependent **diabetes** mellitus (NIDDM), and there is evidence that colonic tone is impaired during hyperglycemia. Sulfonylnrea-**sensitive** potassium channels (KATP) have been identified in various cell types raising the possibility that sulfonylureas, may contribute to colonic dysmotility and constipation in NIDDM. The Authors investigated the effect of glibenclamide, with or without cromakalim, norepinephrine (noradrenaline) and S-nitroso-N-acetylpenicillamine (SNAP), on the contractile properties of longitudinal muscle from the colon of healthy rats. The data suggest that there are KATP channels in rat longitudinal smooth muscle strips. Glibenclamide may modulate the motility of longitudinal muscle strips of the colon by direct effects on open KATP channels or through inhibition of NO. (conference abstract).
ABEX Constipation is common among people with NIDDM, and there is evidence that colonic tone is impaired during hyperglycemia. Sulfonylnrea-**sensitive** potassium channels (KATP) have been identified in various cell types, including smooth muscle cells, raising the possibility that sulfonylureas, used in the treatment of NIDDM, may contribute to colonic dysmotility and constipation in NIDDM. The Authors aim therefore was to investigate the effect of the sulfonylurea, glibenclamide, on the contractile properties of longitudinal muscle from the colon of healthy rats and to further understand the mechanism of this effect. Isolated muscle strips were prepared from the ascending colon of male Sprague-Dawley rats (10-12 wk-old). The effects of 10 nM to 1 uM glibenclamide with or without the KATP channel opener, cromakalim (1 uM to 1 nM), non-epinephrine (1 uM to 10 nM), and the **nitric oxide donor**, S-nitroso-N-acetylpenicillamine (SNAP) (1

uM to 10 n M) were investigated. Glibenclamide had no effect on the spontaneous activity of the colonic longitudinal muscle strips. Cromakalim caused a significant concentration-related inhibition in isolated smooth muscle strips. Glibenclamide, 1 uM, completely prevented the effects of 1 uM cromakalim, and lower concentrations of glibenclamide caused significant shifts in the concentration-response curve to cromakalim. Glibenclamide did not affect the response to carbachol or norepinephrine. Pre-treatment with 1 uM of glibenclamide partially inhibited the inhibitory effect of 1 uM SNAP on spontaneous contractile activity. (LJ)

ACCESSION NUMBER: 1998-45320 DRUGU P
TITLE: Effect and mechanism of glibenclamide on longitudinal smooth muscle contractility in rat colon.
AUTHOR: Choi M G; Camilleri M; Balsiger B M; Farrugia G
LOCATION: Rochester, Minn., USA
SOURCE: Gastroenterology (114, No. 4, Pt. 2, A733, 1998)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Mayo Foundation, Rochester, MN, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
PY **1998**
AB Constipation is common among people with non-**insulin**-dependent **diabetes** mellitus (NIDDM), and there is evidence that colonic tone is impaired during hyperglycemia. Sulfonylnrea-**sensitive** potassium channels (KATP) have been identified in various cell types raising the possibility that sulfonylureas, may contribute to colonic dysmotility. . .
ABEX Constipation is common among people with NIDDM, and there is evidence that colonic tone is impaired during hyperglycemia. Sulfonylnrea-**sensitive** potassium channels (KATP) have been identified in various cell types, including smooth muscle cells, raising the possibility that sulfonylureas, used. . . or without the KATP channel opener, cromakalim (1 uM to 1 nM), non-epinephrine (1 uM to 10 nM), and the **nitric oxide donor**, S-nitroso-N-acetylpenicillamine (SNAP) (1 uM to 10 n M) were investigated. Glibenclamide had no effect on the spontaneous activity of the. . .

L6 ANSWER 21 OF 26 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1996-40330 DRUGU P E
AB I.v. infusion of L-arginine (the precursor of endothelium-derived relaxing factor; EDRF) improved **insulin resistance** in 6 **obese** NIDDM patients. This effect was not based on alterations of **insulin** or IGF-1 levels, nor on altered antilipolytic effects of L-arginine. L-arginine seems to act by an EDRF-dependent mechanism, probably by improvement of endothelial dysfunction (ED). These findings indicate a link between ED and **insulin resistance** and thus might be of particular importance for the development of vascular disease in patients with NIDDM. (conference abstract).
ABEX The study was done in 4 men and 2 women (aged 52 +/- 5 yr, body weight 120 +/- 18 kg, HbA1c 8.9 +/- 1.0%). **Insulin resistance** was assessed twice in each patient by use of the 3 hr **insulin** -suppression test, in absence and presence of concomitant L-arginine infusion (0.52 mg/kg/min). **Insulin** and IGF-1 were measured by RIA. Plasma NOx and FFA were determined photometrically. Mean steady-state plasma glucose was 15.9 +/- 1.1 mmol/l. In the presence of

L-arginine, steady-state plasma glucose was lowered significantly to 13.3 +/- 1.1 mmol/l. Concomitantly slightly increased steady-state plasma NOx level (as an indirect marker for EDRF formation) could be detected (from 53.8 +/- 9 to 67.1 +/- 11 umol/l). Systemic B.P. and steady-state **insulin** were not affected by L-arginine; neither were steady-state levels of IGF-1 or FFA. (E54/RSV)

ACCESSION NUMBER: 1996-40330 DRUGU P E
TITLE: Metabolic effects of intravenous L-arginine in patients with non insulin-dependent **diabetes** mellitus.
AUTHOR: Wascher T C; Graier W F; Bahadori B; Hussain M; Toplak H
CORPORATE SOURCE: Univ.Vienna; Univ.Zurich
LOCATION: Vienna, Austria; Zurich, Switz.
SOURCE: Eur.J.Clin.Invest. (26, Suppl. 1, A40, 1996)
CODEN: EJCIB8 ISSN: 0014-2972
AVAIL. OF DOC.: Department of Internal Medicine, Univ. Graz, Austria.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

TI Metabolic effects of intravenous L-arginine in patients with non insulin-dependent **diabetes** mellitus.

PY **1996**

AB I.v. infusion of L-arginine (the precursor of endothelium-derived relaxing factor; EDRF) improved **insulin resistance** in 6 **obese** NIDDM patients. This effect was not based on alterations of **insulin** or IGF-1 levels, nor on altered antilipolytic effects of L-arginine. L-arginine seems to act by an EDRF-dependent mechanism, probably by improvement of endothelial dysfunction (ED). These findings indicate a link between ED and **insulin resistance** and thus might be of particular importance for the development of vascular disease in patients with NIDDM. (conference abstract).

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CT [01] ARGININE *PH; **DIABETES** *OC; CARBOHYDRATE-METAB.DISORDER *OC; PANCREOPATHY *OC; ARGININE *RN; CASES *FT; IN-VIVO *FT; I.V. *FT; INFUSION *FT; PANCREAS-HORMONE-METAB. *FT; **INSULIN** *FT; CONC. *FT; BLOOD-PLASMA *FT; BLOOD-SUGAR *FT; **NITRIC-OXIDE** *FT; **DONOR** *FT; LIPOLYSIS *FT; SOMATOMEDIN-C *FT; HORMONE-METAB. *FT; STEADY-STATE *FT; **RESISTANCE** *FT; BLOOD-PRESSURE *FT; CONCOMITANT-DISEASE *FT; ENDOTHELIUM *FT; FUNCTION *FT; ENDOTHELIUM-DERIVED-RELAXANT-FACTOR *FT; INJECTION *FT; INJECTION *FT; CARBOHYDRATE-METAB. *FT; LIPID-METAB. *FT; HEMODYNAMICS. . .

L6 ANSWER 22 OF 26 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AB Interleukin-1β (IL-1β) significantly inhibits **insulin** secretion from glucose stimulated islet cells. The mechanism for this inhibition has been hypothesized to be due to stimulation of the inducible form of **nitric oxide** synthase and a resulting increase in **nitric oxide** (NO) concentration. Ways to block the

effect of IL-1β have focused on blocking the binding of IL-1β to the IL-1 receptor and the use of antioxidants to neutralize increases in NO. This report focuses on a 33 residue peptide synthesized based on the C- terminal region of the IL-1β molecule, a reported binding site of the IL- 1β molecule, and the redox-cycling antioxidant pyrroloquinoline quinone (PQQ). The 33 residue peptide did not function as an antagonist, but as a weak **agonist**. High concentrations of PQQ itself inhibited glucose-dependent **insulin** release while low concentrations did not. PQQ had no effect on the actions of IL-1β. Three isosteric and isomeric analogues of PQQ were also investigated. One of the PQQ isomers had an inhibitory effect on **insulin** secretion at low concentrations where PQQ had no effect. These results reflect the **sensitivity** of islets to oxidative stress.

ACCESSION NUMBER: 97019670 EMBASE
DOCUMENT NUMBER: 1997019670
TITLE: Effects of a 33 residue interleukin-1β peptide and the antioxidant PQQ on interleukin-1β-mediated inhibition of glucose-stimulated insulin release from cultured mouse pancreatic islets.
AUTHOR: McInerney M.F.; Seidel M.J.; Nguyen J.M.D.; Flynn J.C.; Sturm N.; Lee H.; Zhang Z.; Tillekeratne L.M.V.; Hudson R.A.
CORPORATE SOURCE: M.F. McInerney, Medicinal/Biological Chemistry Dept., College of Pharmacy, University of Toledo, 2801 W. Bancroft St., Toledo, OH 43606, United States
SOURCE: Research Communications in Molecular Pathology and Pharmacology, (1996) 94/2 (115-128).
Refs: 41
ISSN: 1078-0297 CODEN: RCMPE6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
SO Research Communications in Molecular Pathology and Pharmacology, (1996) 94/2 (115-128).
Refs: 41
ISSN: 1078-0297 CODEN: RCMPE6
AB Interleukin-1β (IL-1β) significantly inhibits **insulin** secretion from glucose stimulated islet cells. The mechanism for this inhibition has been hypothesized to be due to stimulation of the inducible form of **nitric oxide** synthase and a resulting increase in **nitric oxide** (NO) concentration. Ways to block the effect of IL-1β have focused on blocking the binding of IL-1β to the IL-1. . . the redox-cycling antioxidant pyrroloquinoline quinone (PQQ). The 33 residue peptide did not function as an antagonist, but as a weak **agonist**. High concentrations of PQQ itself inhibited glucose-dependent **insulin** release while low concentrations did not. PQQ had no effect on the actions of IL-1β. Three isosteric and isomeric analogues of PQQ were also investigated. One of the PQQ isomers had an inhibitory effect on **insulin** secretion at low concentrations where PQQ had no effect. These results reflect the **sensitivity** of islets to oxidative stress.
CT Medical Descriptors:
***insulin dependent diabetes mellitus**
animal tissue
antioxidant activity

article
drug effect
insulin release
mouse
nonhuman
oxidative stress
pancreas islet
priority journal
*interleukin 1beta
*interleukin derivative: DV, drug development
*interleukin derivative: PD, pharmacology
*pyrroloquinolinequinone: DV,. . .

L6 ANSWER 23 OF 26 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
AN 1998-0261417 PASCAL

AB Several **hypertensive** states are associated with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiological importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, we sought to determine how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist** -stimulated intracellular Ca.sup.2.sup.+ (Ca.sup.2.sup.+.sub.i) transient in VSM cells. In this study, our goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Ca.sup.2.sup.+.sub.iand, if so, to determine whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP. Primary cultured VSM cells from canine femoral artery were bathed in a physiological concentration of extracellular Ca.sup.2.sup.+ and permeabilized to Ca.sup.2.sup.+ with a Ca.sup.2.sup.+ ionophore, either ionomycin or A-23187. The resultant increase in Ca.sup.2.sup.+.sub.i contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Ca.sup.2.sup.+.sub.i or the ionomycin-induced increase in Ca.sup.2.sup.+.sub.i, as determined by fura 2 fluorescence measurements, but it did inhibit ionomycin- and A-23187-induced contractions by 47 and 51%, respectively (both P < 0.05). In the presence of 1.0 μM ionized Ca.sup.2.sup.+, ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP production by 43% (P < 0.05). 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (10 μM), a selective inhibitor of guanylate cyclase that blocked cGMP production in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. It was found that the cells expressed the inducible isoform of NOS. NG-monomethyl-L-arginine or N.sup.G-nitro-L-arginine methyl ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. We conclude that **insulin** stimulates cGMP production and inhibits VSM contraction in the presence of elevated Ca.sup.2.sup.+.sub.i. This inhibition by **insulin** of VSM contraction at sites where Ca.sup.2.sup.+.sub.i could not be rate limiting is dependent on NOS and cGMP.
ACCESSION NUMBER: 1998-0261417 PASCAL

TITLE (IN ENGLISH): **Insulin** inhibits vascular smooth muscle contraction at a site distal to intracellular Ca.sup.2.sup.+ concentration
AUTHOR: KAHN A. M.; HUSID A.; ODEBUNMI T.; ALLEN J. C.; SEIDEL C. L.; SONG T.
CORPORATE SOURCE: Department of Medicine, The University of Texas Health Science Center, Houston, Texas 77030, United States; Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, United States
SOURCE: American journal of physiology. Endocrinology and metabolism, **(1998)**, 37(5), E885-E892, 47 refs.
ISSN: 0193-1849 CODEN: AJPMD9
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-670C1, 354000075847750160

TIEN **Insulin** inhibits vascular smooth muscle contraction at a site distal to intracellular Ca.sup.2.sup.+ concentration

SO American journal of physiology. Endocrinology and metabolism, **(1998)**, 37(5), E885-E892, 47 refs.
ISSN: 0193-1849 CODEN: AJPMD9

AB Several **hypertensive** states are associated with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiological importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, we sought to determine how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist** -stimulated intracellular Ca.sup.2.sup.+ (Ca.sup.2.sup.+.sub.i) transient in VSM cells. In this study, our goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Ca.sup.2.sup.+.sub.iand, if so, to determine whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP. Primary cultured VSM cells from canine femoral artery were bathed in a physiological concentration of extracellular. . . ionomycin or A-23187. The resultant increase in Ca.sup.2.sup.+.sub.i contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Ca.sup.2.sup.+.sub.i or the ionomycin-induced increase in Ca.sup.2.sup.+.sub.i, as determined by fura 2 fluorescence. . . and 51%, respectively (both P < 0.05). In the presence of 1.0 μM ionized Ca.sup.2.sup.+, ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP production by 43% (P < 0.05). 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (10 μM), a selective inhibitor of guanylate cyclase that blocked cGMP production in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. It was found that the cells expressed the inducible isoform of NOS. NG-monomethyl-L-arginine or N.sup.G-nitro-L-arginine methyl ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. We conclude that **insulin** stimulates cGMP production and inhibits VSM contraction in the presence of elevated Ca.sup.2.sup.+.sub.i. This inhibition by **insulin** of VSM contraction at sites where Ca.sup.2.sup.+.sub.i could not be rate

limiting is dependent on NOS and cGMP.
CT Smooth muscle; Muscle contraction; Blood vessel; **Insulin**; **Nitric-oxide** synthase; Guanylate cyclase; Dog; Signal transduction; Target tissue **resistance**
CTFR Muscle lisse; Contraction musculaire; Vaisseau sanguin; Insuline; **Nitric-oxide** synthase; Guanylate cyclase; Chien; Transduction signal; **Resistance** tissu cible
CTES Musculo liso; Contraccion muscular; Vaso sanguineo; Insulina; **Nitric-oxide** synthase; Guanylate cyclase; Perro; Transduccion senal; **Resistencia** tejido blanco

L6 ANSWER 24 OF 26 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
AN 1996-0298684 PASCAL

AB Purpose : This study was performed to examine the role of the vascular endothelium in modulating arterial reactivity to adrenergic vasoconstriction in subcutaneous arteries from patients with type II **diabetes**. Methods : Small subcutaneous arteries (inner diameter = 90 to 180 μm) from control subjects (n = 22) and patients with **diabetes** (n = 18) were dissected from skin biopsies obtained at surgery and mounted on a specialized arteriograph that allowed for continuous measurement of lumen diameter under controlled pressure. The **sensitivity** to norepinephrine was compared in arteries that were either intact, denuded of endothelium, or intact and exposed to Nω-nitro-L-arginine (L-NNA), an inhibitor of **nitric oxide** synthesis. Stimulated release of **nitric oxide** by acetylcholine and smooth muscle cell responses to sodium nitroprusside were also evaluated in **diabetic** and control arteries. Results : **Sensitivity** to norepinephrine was augmented in **diabetic** arteries and the amount of **agonist** necessary to contract the vessels 50% of maximum (EC.sub.5.sub.0) decreased from 0.35 ± 0.05 μmol/L in the control arteries to 0.16 ± 0.06 μmol/L in the **diabetic** arteries ($p < 0.05$). Both endothelial removal and blockade of **nitric oxide** synthesis increased **sensitivity** to norepinephrine in control arteries (EC.sub.5.sub.0.sub.d.sub.e.sub.n.sub.u.sub.d.sub.e.sub.d = 0.14 ± 0.03 μmol/L and EC.sub.5.sub.0.sub.L.sub.-.sub.N.sub.N.sub.A = 0.14 ± 0.04 μmol/L ; $p < 0.01$) but failed to augment **sensitivity** in **diabetic** arteries (EC.sub.5.sub.0.sub.d.sub.e.sub.n.sub.u.sub.d.sub.e.sub.d = 0.17 ± 0.05 μmol/L and EC.sub.5.sub.0.sub.L.sub.-.sub.N.sub.N.sub.A = 0.15 ± 0.04 μmol/L ; $p > 0.05$). Stimulated release of **nitric oxide** by acetylcholine was increased in the **diabetic** arteries : EC.sub.5.sub.0.sub.c.sub.o.sub.n.sub.t.sub.r.sub.o.sub.l = 0.04 ± 0.01 μmol/L versus EC.sub.5.sub.0.sub.d.sub.i.sub.a.sub.b.sub.e.sub.t.sub.i.sub.c = 0.009 ± 0.001 μmol/L ($p < 0.05$). **Sensitivity** of vascular smooth muscle to sodium nitroprusside was similar in both nondiabetic and **diabetic** arteries. Conclusions : The endothelium mitigates adrenergic reactivity in control arteries, which is lacking in **diabetic** arteries and results in enhanced reactivity to norepinephrine ; increased **sensitivity** of **diabetic** arteries to acetylcholine, however, indicates a possible alteration at the receptor level.
ACCESSION NUMBER: 1996-0298684 PASCAL

TITLE (IN ENGLISH): Endothelial function and adrenergic reactivity in human type-II **diabetic resistance**

arteries

AUTHOR: CIPOLLA M. J.; HARKER C. T.; PORTER J. M.
CORPORATE SOURCE: Department of Surgery, Division of Vascular Surgery, Oregon Health Sciences University, Portland, Ore., United States

SOURCE: Journal of vascular surgery, **(1996)**, 23(5), 940-949, 31 refs.
Conference: Joint Meeting of the Society of Vascular Surgery and the International Society for Cardiovascular Surgery, New Orleans, La. (United States), 11 Jun 1995
ISSN: 0741-5214 CODEN: JVSUES
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-20352, 354000043740550260

TIEN Endothelial function and adrenergic reactivity in human type-II **diabetic resistance** arteries

SO Journal of vascular surgery, **(1996)**, 23(5), 940-949, 31 refs.
Conference: Joint Meeting of the Society of Vascular Surgery and the International Society for Cardiovascular Surgery, New. . .

AB. . . role of the vascular endothelium in modulating arterial reactivity to adrenergic vasoconstriction in subcutaneous arteries from patients with type II **diabetes**. Methods : Small subcutaneous arteries (inner diameter = 90 to 180 μm) from control subjects (n = 22) and patients with **diabetes** (n = 18) were dissected from skin biopsies obtained at surgery and mounted on a specialized arteriograph that allowed for continuous measurement of lumen diameter under controlled pressure. The **sensitivity** to norepinephrine was compared in arteries that were either intact, denuded of endothelium, or intact and exposed to Nω-nitro-L-arginine (L-NNA), an inhibitor of **nitric oxide** synthesis. Stimulated release of **nitric oxide** by acetylcholine and smooth muscle cell responses to sodium nitroprusside were also evaluated in **diabetic** and control arteries. Results : **Sensitivity** to norepinephrine was augmented in **diabetic** arteries and the amount of **agonist** necessary to contract the vessels 50% of maximum (EC.sub.5.sub.0) decreased from 0.35 ± 0.05 μmol/L in the control arteries to 0.16 ± 0.06 μmol/L in the **diabetic** arteries ($p < 0.05$). Both endothelial removal and blockade of **nitric oxide** synthesis increased **sensitivity** to norepinephrine in control arteries (EC.sub.5.sub.0.sub.d.sub.e.sub.n.sub.u.sub.d.sub.e.sub.d = 0.14 ± 0.03 μmol/L and EC.sub.5.sub.0.sub.L.sub.-.sub.N.sub.N.sub.A = 0.14 ± 0.04 μmol/L ; $p < 0.01$) but failed to augment **sensitivity** in **diabetic** arteries (EC.sub.5.sub.0.sub.d.sub.e.sub.n.sub.u.sub.d.sub.e.sub.d = 0.17 ± 0.05 μmol/L and EC.sub.5.sub.0.sub.L.sub.-.sub.N.sub.N.sub.A = 0.15 ± 0.04 μmol/L ; $p > 0.05$). Stimulated release of **nitric oxide** by acetylcholine was increased in the **diabetic** arteries : EC.sub.5.sub.0.sub.c.sub.o.sub.n.sub.t.sub.r.sub.o.sub.l = 0.04 ± 0.01 μmol/L versus EC.sub.5.sub.0.sub.d.sub.i.sub.a.sub.b.sub.e.sub.t.sub.i.sub.c = 0.009 ± 0.001 μmol/L ($p < 0.05$). **Sensitivity** of vascular smooth muscle to sodium nitroprusside was similar in both nondiabetic and **diabetic** arteries. Conclusions : The endothelium mitigates adrenergic reactivity in control arteries, which is lacking in **diabetic** arteries and results in enhanced reactivity to norepinephrine ; increased **sensitivity** of **diabetic** arteries to acetylcholine, however, indicates a possible

alteration at the receptor level.
CT Non **insulin** dependent **diabetes**; Vasoconstriction; Norepinephrine; Endothelium; Exploration; Human
CTFR **Diabete** non insulinodependant; Vasoconstriction; Noradrenaline; Endothelium; Exploration; Homme
CTES **Diabetes** no insulinodependiente; Vasoconstriccion; Endotelio; Exploracion; Hombre

L6 ANSWER 25 OF 26 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AB Several **hypertensive** states are associated with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiological importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, we sought to determine how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist**-stimulated intracellular Ca2+ (Ca-i(2+)) transient in VSM cells. In this study, our goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Ca-i(2+) and, if so, to determine whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP Primary cultured VSM cells from canine femoral artery were bathed in a physiological concentration of extracellular Ca2+ and permeabilized to Ca2+ with a Ca2+ ionophore, either ionomycin or A-23187. The resultant increase in Ca-i(2+) contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Ca-i(2+) or the ionomycin-induced increase in Ca-i(2+), as determined by fura 2 fluorescence measurements, but it did inhibit ionomycin-and A-23187-induced contractions by 47 and 51%, respectively (both $P < 0.05$). In the presence of 1.0 mu M ionized C-a2+ ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP production by 43% ($P < 0.05$). 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (10 mu M), a selective inhibitor of guanylate cyclase that blocked cGMP production in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. It was found that the cells expressed the inducible isoform of NOS. N-G-monomethyl-L-arginine or N-G-nitro-L-arginine methyl ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. We conclude that **insulin** stimulates cGMP production and inhibits VSM contraction in the presence of elevated Ca-i(2+) This inhibition by **insulin** of VSM contraction at sites where Ca-i(2+) could not be rate limiting is dependent on NOS and cGMP.
ACCESSION NUMBER: 1998:367309 SCISEARCH
THE GENUINE ARTICLE: ZM052
TITLE: Insulin inhibits vascular smooth muscle contraction at a site distal to intracellular Ca2+ concentration
AUTHOR: Kahn A M (Reprint); Husid A; Odebunmi T; Allen J C; Seidel C L; Song T
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, DEPT MED, 4-138 MSB, POB 20708, HOUSTON, TX 77030 (Reprint); BAYLOR COLL MED, DEPT MED, HOUSTON, TX 77030
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-ENDOCRINOLOGY AND METABOLISM, (**MAY 1998**) Vol. 37, No. 5, pp. E885-E892.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE,

BETHESDA, MD 20814.
ISSN: 0193-1849.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

SO AMERICAN JOURNAL OF PHYSIOLOGY-ENDOCRINOLOGY AND METABOLISM, (**MAY 1998**) Vol. 37, No. 5, pp. E885-E892.
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AB Several **hypertensive** states are associated with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiological importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, we sought to determine how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist**-stimulated intracellular Ca2+ (Ca-i(2+)) transient in VSM cells. In this study, our goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Ca-i(2+) and, if so, to determine whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP Primary cultured VSM cells from canine femoral artery were bathed in a physiological concentration of extracellular. . . ionomycin or A-23187. The resultant increase in Ca-i(2+) contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Ca-i(2+) or the ionomycin-induced increase in Ca-i(2+), as determined by fura 2 fluorescence. . . 51%, respectively (both $P < 0.05$). In the presence of 1.0 mu M ionized C-a2+ ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP production by 43% ($P < 0.05$). 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (10 mu M), a selective inhibitor of guanylate cyclase that blocked cGMP production in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. It was found that the cells expressed the inducible isoform of NOS. N-G-monomethyl-L-arginine or N-G-nitro-L-arginine methyl ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. We conclude that **insulin** stimulates cGMP production and inhibits VSM contraction in the presence of elevated Ca-i(2+) This inhibition by **insulin** of VSM contraction at sites where Ca-i(2+) could not be rate limiting is dependent on NOS and cGMP.

STP KeyWords Plus (R): NITRIC-OXIDE SYNTHASES; PROTEIN-KINASE; BLOOD-FLOW; RAT-KIDNEY; CALCIUM; CELLS; RELAXATION; INDUCTION; **HYPERTENSION**; HYPOTHESIS

L6 ANSWER 26 OF 26 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

AB We have previously used the comet assay to demonstrate that the **nitric oxide donor** 3-morpholinosydnonimine (SIN-I) produces DNA damage in rat islets of Langerhans and in the SV40-transformed **insulin**-secreting hamster cell line, HIT-T15. Damage is not prevented by the addition of superoxide dismutase (SOD). In the present study, we have compared SIN-1, which generates **nitric oxide**, superoxide anion and hydrogen peroxide, with two other

nitric oxide donors, S-nitrosoglutathione (GSNO) and the tetra-iron-sulphur cluster nitrosyl, Roussin's black salt (RES). We have used the comet assay as a highly **sensitive** method to measure DNA-damaging ability, and also measured inhibition of DNA synthesis and inhibition of **insulin** secretion. We have examined the effect of SOD and catalase on each of these endpoints in HIT-T15 cells following a 30-min exposure to the compounds (24 h for DNA synthesis), All compounds produced a significant dose-dependent increase in strand-breakage formation and all inhibited DNA synthesis and glucose-stimulated **insulin** secretion. RES was the most potent. SOD did not reduce the responses observed with any of the compounds. Catalase largely prevented DNA strand breakage, inhibition of DNA synthesis and inhibition of **insulin** secretion by SIN-1, but had no effect on responses to GSNO or RES. Addition of SOD together with catalase gave no greater protection against SIN-1 than catalase alone, The **nitric oxide** and superoxide anion produced by SIN-1 are thought to combine to form highly reactive peroxynitrite. In addition, H2O2 may be formed in the presence of SIN-1 and may form hydroxyl radical in the presence of a transition metal, such as Fe2+. It appears that in **insulin**-secreting cells, the effects of SIN-1 are largely mediated by this latter mechanism. In contrast, GSNO and RES appear to act by a different mechanism, not overtly involving reactive oxygen species. GSNO and H2O2 show no significant interaction in the induction of DNA strand breaks. Both **nitric oxide** and H2O2 are effective, directly or indirectly, as DNA strand-breaking agents, inhibitors of DNA synthesis and inhibitors of **insulin** secretion.

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STP KeyWords Plus (R): RAT PANCREATIC-ISLETS; HYPOXANTHINE XANTHINE-OXIDASE; DEPENDENT **DIABETES**-MELLITUS; SUPEROXIDE-DISMUTASE; HYDROGEN-PEROXIDE; CYCLIC-GMP; BIOLOGICAL DAMAGE; ACTIVE OXYGENS; L-ARGININE; INTERLEUKIN-1-BETA

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